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JACOBSON PRICE HOLMAN AND STERN
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400 SEVENTH STREET NW
WASHINGTON, DC 200042201

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CRANE, LAWRENCE E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/796,040	Applicant(s) Colpan	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE --3-- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on -03/26/02 (Response)-.
[X] This action is **FINAL.**
[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims —101-119— are pending in the application. Claims -[]- have been cancelled.
Of the above claim(s) —[]— is/are withdrawn from consideration.
[] Claim(s) —[]— is/are allowed.
[X] Claims —101-119— are rejected.
[] Claim(s) —[]— is/are objected to.
[] Claim(s) —[]— are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
[] The proposed drawing correction, filed on -[]- are [] approved [] disapproved.
[] The drawing(s) filed on -[]- is/are objected to by the Examiner.
[] The specification is objected to by the Examiner.
[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
[X] All [] Some* [] None of the CERTIFIED copies of the priority documents have been
[] received.
[] received in Application No. (Series Code/Serial Number) -[]-.
[X] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: -[]-.

Attachment(s)

[] Information Disclosure Statement(s), PTO-1449, Paper No(s). —[]—
[] Notice of Reference(s) Cited, PTO-892
[] Notice of Draftsperson's Patent Drawing Review, PTO-948
[] Interview Summary, PTO-413
[] Notice of Informal Patent Application, PTO-152
[] Other: -[]-.

No amendments have been submitted in the response filed March 26, 2002.

Claims **101-119** remain in the case.

Claim **117** is rejected under 35 U.S.C. §112, first paragraph, as the disclosure is enabling only for claims wherein the scope of the claimed subject matter is commensurate in scope with disclosed specific embodiments directed to nucleic acid purifications using a single adsorbent only and where alcoholic precipitating solutions do not contain more than three components. See MPEP 706.03(n) and 706.03(z).

In claim **117**, the term "or mixture thereof" is lacking in proper enablement as no teachings are found which disclose how to use any more than one of the vast array of pH adjusted binary and ternary mixtures of ionic solutes and cosolvents being claimed when practicing the claimed invention. The use of higher order pH adjusted solvent/solute mixtures is not taught herein in any specific embodiment.

Applicant's arguments filed March 26, 2002 have been fully considered but they are not persuasive.

Applicant has explained at great length and in detail what the term "and mixture thereof" is intended to refer to. Applicant is respectfully encouraged to amend the claim to make this unambiguously clear; e.g. amend the term
" in a 20% ethanol, propanol, isopropanol, butanol, or polyethylene glycol, or mixture thereof " to read

-- in a 20% alcoholic solution wherein the alcoholic portion is selected from the group consisting of ethanol, propanol, isopropanol, butanol, ~~or~~ polyethylene glycol ~~or~~ and mixtures thereof --.

Claim **117** is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **117**, at lines 4-5, the structure of the claim is also made indefinite by term "or mixture thereof." It is unclear what combinations of solutes and cosolvents are actually being claiming. T

Applicant's arguments filed March 26, 2002 have been fully considered but they are not persuasive.

Applicant is respectfully requested to note the suggestion advanced in the comments following the previous rejection.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **101-119** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Henco et al. '426** (PTO-892 ref. **I**)in view of **Little '430** (PTO-1449 ref. **AC**) and further in view of International Dictionary of Medicine and Biology (PTO-892 ref. **S**) and **Hames et al.** (PTO-892 ref. **R**).

The instant claims are directed to a process for DNA purification with the following steps:
i) cell lysis using an enzyme (e.g. Rnase A) or using a mixture of chemical reagents (e.g. buffered SDS) and debris removal using filtration and/or centrifugation;
ii) contacting the filtrate from step i) with an anion exchange resin in buffers of low ionic strength, and elution of the DNA from the anion exchange resin by contacting with a high-ionic-strength buffer, optionally following the addition of a lower alcohol, or of polyethylene glycol, and
iv) desalting the DNA-containing solution by contacting same with a mineral support material to effect adsorption of the DNA onto the mineral support material (e.g silica gel) followed by washing the adsorbed DNA with alcoholic solutions to remove salts, and elution of DNA from the mineral adsorbent by contacting the mineral support material with a low ionic strength buffer (e.g. buffered Tris) or with water.

Henco et al. '426 discloses a four step process summarized as follows:
i) cell lysis/filtration by any one of numerous known methods including the use of detergents, proteolytic enzymes or mechanical procedures (see claim 8) including centrifugation (see column 6, lines 51-66);
ii) anion exchange chromatography by transferring the product solution from step i) to an anion exchange resin followed by washing with a low ionic strength buffer the intended effect of which is to remove all of the interfering substances (e.g. RNA, proteins) from long chain DNA which remains adsorbed on the column optionally in the presence of known DNA precipitants polyethylene glycol or isopropanol (see col. 12, lines 41-42);

iii) elution of the long chain DNA from the anion exchange column adsorbent with high ionic strength buffer; and
iv) desalting the DNA by one of several different methods. One method of desalting not mentioned in the Henco disclosure is adsorption chromatography wherein a sample of DNA is applied to the column adsorbent such as silica gel in the presence of a high ionic strength buffer and separated therefrom by subsequent elution with low ionic strength buffer or water alone.

Little '430 at column 7, lines 12-45, discloses one of several examples wherein DNA is extracted from cells of various types using chaotropic ion/enzyme-mediated digestion followed by centrifugation and ultimately chromatographic separation using a commercial diatomaceous earth (Celite™) and various buffer solutions. As noted in the abstract, Little discloses the application of DNA to the adsorbent from a relative high ionic strength solution, washing to remove salts, and subsequent elution of the adsorbed DNA with a low ionic strength buffer or with water. This reference does not disclose the use of anion exchange resins to selectively retain DNA in a purification process.

To make clear the meaning of the **Henco et al. '426** disclosure two additional definitional references have been cited along with the relevant portion of Henco to provide a more complete basis for the instant rejection. The term "chaotropic" is defined in International Dictionary of Medicine and Biology, Vol. 1, at p. 522 to be a word describing an agent which " ... destroys the the order of water when dissolved in it and thereby raises the solubility of hydrophilic substances in the solution." Further definitional exemplification is provided by **Hames et al.** (Nucleic Acid Hybridisation - A Practical Approach) via the indexing of "Chaotropic agents" at p. 235, which refers to pages 64-65 wherein a list of compounds is provided at p. 65, lines 10-12 and

includes i) ethylene glycol, ii) sodium perchlorate, iii) tetramethylammonium chloride, iv) tetraethylammonium chloride and v) urea. (emphais added) The Henco reference does not make any generic reference to "chaotropic agents," but at column 8, line 61 Henco specifies "urea" as a component of the viral lysis mixture.

Applicant's combination of,
a) conventional cell lysis,
b) the physical separation of cell debris,
c) the anionic exchange chromatography of the filtrate isolated from the cell debris, and
d) finally desalting of the DNA-containing eluate form the anion exchange column by application to a chromatographic adsorbent (e.g. silica gel) to effect the desalting,
is a combination of process steps well known in the prior art and motivated generically by the disclosures of **Henco et al. '426**, with specific desalting step details disclosed by the **Little '430** reference. As noted supra, Henco does teach the use of DNA desalting subsequent to anion exchange. The failure to teach the specific desalting method of the instant claimed method by **Henco '426** has been addressed in the instant rejection of record by combining **Henco et al. '426** with the **Little '430** reference, wherein the latter reference discloses the utility of classical chromatography adsorbents for the purpose of isolating purified DNA in solutions with low net ionic strength. For this reason applicant's claimed process has been found to be nothing more than a combination of the **Henco '426** reference with **Little et al.'430**, wherein Henco provides the motivation to combine by noting the need to desalt the high-ionic-strength solution of DNA produced by anion exchange chromatography (see column 7, lines 44-46; or col. 12, lines 42-43). The specific details of washing steps, the timing of steps, the

specific selection of wash solution contents, and the physical characteristics of the anion exchange resin and mineral adsorbent (e.g., particle diameter, pore size, etc.) are deemed to be variables clearly within the purview of the ordinary practitioner seeking to optimize the Henco and Little process steps for a specific situation. Therefore, the details of adsorbent choice, or other standard performance parameters (e.g. the frequency of washes, the variation of ionic strength in wash solutions, etc.) are deemed to be the kind of variables properly within the realm of routine experimentation by an ordinary practitioner in the course of optimizing the process steps disclosed in the prior art of record. For these reasons, the instant claims, in so far as they are directed to routine changes in experimental details of the kind noted above, are deemed to lack an adequate basis for a finding of patentable distinction for any variation of the instant claimed process, as such variations are deemed to have been properly included within the scope of the noted prior art.

Therefore, the instant claimed process for DNA purification by anion exchange chromatography followed by desalting using an entirely conventional adsorption chromatographic process would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed March 26, 2002 have been fully considered but they are not persuasive.

As a preliminary matter, the above rejection is based on 35 U.S.C. §103(a) (obviousness), and is therefore <u>not</u> an anticipation rejection. Therefore, secondary references are not properly found by applicant to be incomplete on the basis of an anticipation-type analysis.

Applicant argues generally that the instant combination of **Henco '426** and **Little '430** is not properly motivated and therefore not a proper basis for rejection of the instant claims. Examiner respectfully disagrees. As delineated in detail in the rejection supra, the **Henco '426** reference discloses generically all of the process steps claimed herein. The **Little '430** reference, the International Dictionary of Medicine and Biology reference, and **Hames** reference are cited to specifically describe how to carry out the generically taught portions of **Henco '426** or to provide definitions to make plain that the steps in **Henco '426** have been properly found by instant Examiner to read on the instant claimed process steps.

Applicant argues at page 7 of the response that

"[no] hint is given in Henco that (i) an increase in salt concentration should be effected in the sample fraction, nor is there any hint that (ii) such a fraction should be subsequently treated by application to a mineral support material in order to bind thereto the nucleic acid contained in the fraction, nor is there any hint to (iii) subsequently elute the substrate-bound nucleic acids using a buffer having a very low ionic strength."

Examiner respectfully disagrees with this line of argument. Examiner notes that Henco at column 7, line 45, discloses that following anion exchange chromatography (see column 5, lines 37-40 and column 7, lines 15-20), that "DNA may be desalted ... ." It is this teaching which clearly motivates one of ordinary skill to combine the Henco '426 disclosure with Little '430, because it opens the door to optional application of desalting processes including that of Little. Thus, while applicant is correct in pointing out that Henco does not disclose the

particulars of instant process steps c) and d), it does permit combination with Little '430 wherein the details of desalting of DNA using adsorption chromatography are provided.

Applicant argues at the top of page 8 of the instant response that "Little provides no teaching or suggestion to supply the salient deficiencies in Henco." Examiner respectfully disagrees, noting at column 2, lines 24-31, that Little'430 discloses " ... a process for the purification of ... DNA which comprises a) immobilizing the DNA onto diatomaceous earth in the presence of a chaotropic agent; ... and d) eluting the DNA with a low salt buffer or water." This quotation from Little '430 is deemed by examiner to include the essence of steps c) and d).

Applicant then avers that he " could not find any passage in the while disclosure of Little that nucleic acids, ***which have already been separated,*** should be subject to a treatment according to Little." (emphasis in original) Examiner respectfully disagrees, and counters with the argument that applicant's assertion is beside the point. Little '430 is cited only to supply the details of a methods of desalting a DNA containing sample by adsorption chromatography, a step optionally provided for by Henco. Applicant appears to be applying an anticipation standard (e.g. suggesting that Little '430 does not anticipate the instant claims) when such a standard is inappropriate.

Applicant at the end of the second paragraph of page 8 of the instant response argues that Henco '426 fails to disclose the " ... use of any material for being a chaotropic salt." Examiner finds this statement puzzling, but assumes that applicant is referring to the use of chaotropic materials to effect cell lysis, a process clearly disclosed in Henco '426 at

column 8, at lines 60-63 ("urea, detergent and buffer") although the chaotrope used (urea) is not a salt.

Applicant at page 8, last paragraph, is arguing a point without making reference to any particular step in the claimed process. Examiner assumes that applicant is referring to the elution of DNA in step b) wherein ion exchange chromatography requires a high ionic strength buffer to effect DNA elution. This is provided for in Henco '426 at column 7 at lines 18-19.

Applicant then argues in the paragraph spanning pages 8 and 9 of the instant response that "[b]oth the idea and the means to achieve the idea must be evidenced in the prior art in order to demonstrate lack of patentability." Examiner agrees, noting that Henco '426 discloses cell lysis, DNA separation by ion exchange chromatography and optional subsequent desalting, i.e. all of the basic process steps claimed herein. While Henco '426 does not disclose the particular method of desalting relied on herein, this shortcoming is made up for by combination of Henco '426 with the disclosure of Little '430, a combination clearly motivated by the disclosure of Henco.

Applicant argues in the paragraph bridging pages 9 and 10 of the response "[t]hat optional desalting is taught in Henco .. is not disputed, [Henco] fail[s] to support the allegation that the skilled artisan would have been motivated to rely on Little's process in order to 'desalt' Henco's sample." Examiner respectfully disagrees. While it is correct that Henco lists three methods of desalting none of which are the method of Little '430, this does not bar the ordinary practitioner conducting routine experimentation to optimize the prior art from seeking other methods of desalting DNA known in the art including the method of Little '430.

Applicant argues in the paragraph bridging pages 10 and 11 that Little '430 differs from Henco '426 in the area of salt content of the initial DNA sample, and therefore appears to be again incorrectly applying anticipation analysis.

Applicant argues in the first full paragraph of page 11 that the Little '430 reference is directed to "a process for the *purification* of plasmid and other DNA ..." (emphasis added by applicant), noting that high salt concentration was merely a detail required by the Little process. Examiner agrees, noting that Henco '426 optionally teaches desalting, a process step which represents additional DNA *purification*.

Applicant argues in the second full paragraph of page 11 that the rejection of record included impermissible hindsight reconstruction, asserting that "Little is not concerned in any way with desalting of a sample," but that "Little is concerned with purification of DNA found in a high salt solution" and that "Henco ... does not yield such a sample having nucleic acid in a high salt environment." Examiner respectfully disagrees with this analysis. Clearly, Henco '426 does yield a high salt content DNA sample as a direct consequence of the high salt elution conditions required to remove DNA from an anion exchange chromatography. And, applicant's word analysis of Little '430 does not mean that Little is not directed to a method of DNA purification which may be used to desalt DNA samples. Therefore, because applicant's argument is based on at least one factually incorrect assertion, examiner finds the instant argument to be fatally flawed.

In the paragraph bridging pages 11 and 12, applicant alleges that the rejection "makes it *appear* as if Little encompasses (that is *contemplated*) using *isolated* DNA as a starting material." (emphasis in

original) Examiner respectfully disagrees. As applicant noted in the previous paragraph, "Little is concerned with purification of DNA found in a high salt solution." Therefore, it appears that applicant has already agreed that the the Little '430 reference is applicable to the purification of DNA samples without any particular limitation as the source or degree of DNA purity.

Applicant argues, in the last paragraph of page 12 and the first paragraph of page 13, that the combination of references is incorrect apparently because "[i]f there were any motivation, it would have been to *replace* the Henco method, entirely, with the Little method." Examiner respectfully disagrees, and does not elect to change the basis of the instant rejection.

Applicant argues again, in the second paragraph of page 13 of the instant response, that the instant rejection relies on impermissible hindsight reconstruction by "selectively picking and choosing from Little's teachings." Examiner respectfully disagrees, noting that Little is cited because it is directed to a method of DNA purification that has the effect of desalting the DNA sample, which is the very essence of Little's method.

In the third paragraph of page 13 of the instant response, applicant argues that the suggested combination " ... would destroy the invention upon which Little was based; that is, for example a *one*-step procedure to save time." Examiner respectfully disagrees, noting that the complete method of Little '430 is used as is as a method of desalting as provided for in Henco '426 as an optional last process step.

Beginning at the bottom of page 13 and continuing on page 14, applicant argues that the *International Dictionary* and Hames references

are improperly relied on for the definition of chaotrope, aka denaturing agent and compounds with this characteristic in water. In particular applicant argues that " ... Henco neither teaches nor suggests use of these [chaotropic] materials for their allegedly chaotropic function." Examiner respectfully disagrees, noting that "chaotropic" according to the *International Dictionary* is not a black and white characteristic but a characteristic of water soluble compounds, typically ions, which have the effect of " ...destroying the order of water" in varying degrees; i.e. chaotropic power varies according to the solute used. Examiner also notes that the effect noted is also described in Hames as a result of desolving "Denaturing Agents" in water, and that these "Agents" include both perchlorate salts (specifically mentioned in the *International Dictionary* definition of "chaotropic) and neutral substances including ethylene glycol and urea. Therefore, Henco '426 use of a combination of "urea, detergent and buffer" to effect lysis of CMV viruses (column 8, lines 60-62) is plainly an example where two of the three components of the lysis buffer are chaotropic (urea and detergent), a reality which the lysis buffer relies on to effect the cell wall lysis. Examiner concludes that applicant's argument is not convincing because there is no requirement that the prior art use any particular term to specify an effect when the ordinary practitioner would know of the effect in the absence of the presence of the specific term.

In the first paragraph of page 15, applicant argues that "the teachings of Little, as a whole, not merely those of Little's claims that must be applied to the presently claimed invention for purposes of analysis under § 103 of the statute." Examiner respectfully disagrees, noting that review of the above grounds of rejection has failed to produce any reference to the claims of Little '430. For this reason

Examiner finds applicant's argument to be erroneous because it assumes a fact not found in the rejection supra.

In the second paragraph of page 15 applicant argues that "[t]he statement of rejection mischaracterizes Applicant's arguments as based on destroying " ... the motivation provided by Henco." Examiner respectfully disagrees, noting that review of the above grounds of rejection has failed to produce any reference to the alleged criticism.

For the above reasons, applicant's arguments, taken individually or taken as a whole, have not been found convincing, and therefore the instant grounds of rejection have been maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Johann Richter, can be reached at (703)-308-4532.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
08/06/02

JAMES O. WILSON
PRIMARY EXAMINER
GROUP 1600

Johann Richter, Ph.D., Esq.
Supervisory Patent Examiner
Technology Center 1600